CLAIMS

1. A method of inducing tolerance to an antigen in a patient, the method comprising administering to the patient an agent which raises the effective cAMP concentration in a monocyte cell and granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof.

2. A method according to Claim 1 wherein the agent which raises the effective cAMP concentration in a monocyte cell is any one or more of a prostaglandin or agonist thereof, a β-adrenergic agent, a blocker of cAMP export from the cell, forskolin or a derivative thereof, a cAMP phosphodiesterase inhibitor, a cAMP analogue, or cholera toxin or a derivative or fragment thereof.

3. A method according to Claim 2 wherein the blocker of cAMP export from the cell is probenicid or progesterone.

4. A composition according to Claim 2 wherein the cAMP analogue is Sp-adenosine 3′,5′-cyclic monophosphorothioate or 8-bromoadenosine 3′,5′ cyclic monophosphate or dibutryryl cAMP.

5. A method according to Claim 2 wherein the prostaglandin or agonist thereof stimulates cAMP production in a monocyte.

6. A method according to Claim 2 or 5 wherein the prostaglandin or agonist thereof is any one of a prostaglandin E, such as prostaglandin E_2 or an analogue thereof, dinoprostone, gemeprost, misoprostol, alprostadil, limaprost, butaprost, 11-deoxy PGE1, AH23848, AH13205; or a 19-hydroxy PGE.

7. A method according to any of Claims 1 to 6 wherein the GMCSF is human GMCSF having the amino acid sequence as defined in Figure 1, or naturally occurring variants thereof.

8. A method according to any of Claims 1 to 6 wherein the GMCSF is sargramostim.

9. A method according to any of Claims 1 to 6 further comprising administering a monocyte chemotactic agent to the patient.

10. A method according to Claim 9 wherein the monocyte chemotactic agent is MCP-1 or MIP-1α.

11. A method according to any of Claims 1 to 10 further comprising administering a PDE inhibitor to the patient.

12. A method according to Claim 11 wherein the PDE inhibitor is any one of 3-isobutyl-1-methylxanthine (IBMX), pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione), rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone), theophylline, or denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine).

13. A method according to Claim 11 or 12 wherein the PDE inhibitor is selective for type IV PDE.

14. A method according to Claim 13 wherein the PDE inhibitor selective for type IV PDE is any one of rolipram (4-[3-cyclopentyloxy-4-

methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone), denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine), or CDP840, RP73401 or RS33793.

15. A method according to any one of Claims 1 to 14 further comprising administering the antigen or a derivative thereof to the patient.

16. A method according to any one of Claims 1 to 15 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is administered locally at a site where tolerance is required.

17. A method according to any one of Claims 1 to 16 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is administered systemically.

18. A method according to Claim 17 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is administered orally.

19. A method according to Claim 17 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the

PDE inhibitor and the antigen or derivative thereof is administered as a suppository or capsule.

20. A method according to Claim 19 wherein the suppository or capsule has an enteric coating for release of the one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof in the bowel of the patient.

21. A method according to Claim 17 wherein at least the GMCSF or derivative thereof is administered subcutaneously or intravenously.

22. A method according to any one of Claims 1 to 21 wherein any two or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof are administered simultaneously.

23. A method according to any one of Claims 1 to 22 for combating a disease or condition associated with transplant rejection.

24. A method according to Claim 23 wherein the disease or condition associated with transplant rejection comprises graft versus host disease or host versus graft disease.

25. A method according to Claim 23 or 24 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic

agent, the PDE inhibitor and the antigen or derivative thereof is administered is administered prior to the transplant.

26. A method according to any one of Claims 23 to 25 wherein the antigen is HLA-A2.

27. A method according to any one of Claims 1 to 22 for treating an autoimmune disease or condition.

28. A method according to Claim 27 wherein the autoimmune disease is selected from primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastris, Addison's disease, insulin-dependent diabetes mellitus (IDDM), Goodpasture's syndrome, myasthenia gravis, sympathetic ophthalmia, multiple sclerosis (MS), autoimmune haemolytic anaemia, idiopathic leucopenia, ulcerative colitis, dermatomyositis, scleroderma, mixed connective tissue disease, rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythromatosus (SLE), Hashimoto's disease, thyroiditis, Behcet's disease, coeliac disease/dermatitis herpetiformis, renal vasculitis and demyelinating disease.

29. A method according to Claim 27 or 28 wherein the antigen is a self-antigen.

30. A method according to any one of Claims 27 to 29, wherein if the autoimmune disease is pernicious anaemia, the antigen is vitamin B_{12}; if the disease is Addison's disease, the antigen is adrenal antigen; if the disease is IDDM, the antigen is glutamic acid decarboxylase (GAD), insulin, or IA-2; if the disease is Goodpasture's syndrome or renal vasculitis, the antigen is renal antigen or endothelial antigen; if the

disease is myasthenia gravis, the antigen is the acetyl choline receptor; if the disease is sympathetic ophthalmia, the antigen is ocular antigen; if the disease is multiple sclerosis (MS), the antigen is myelin basic protein (MBP), proteolipid protein (PLP), or myelin oligodendrocyte glycoprotein (MOG); if the disease is autoimmune haemolytic anaemia, the antigen is red cell antigen; if the disease is idiopathic leucopenia, the antigen is leukocyte antigen; if the disease is ulcerative colitis, the antigen is a food antigen or a viral antigen; if the disease is dermatomyositis, the antigen is smooth muscle antigen; if the disease is scleroderma, the antigen is a connective tissue antigen; if the disease is mixed connective tissue disease, the antigen is a connective tissue antigen; if the disease is irritable bowel syndrome, the antigen is a food antigen; if the disease is systemic lupus erythmatosus (SLE), the antigen is a histone protein or immunoglobulin heavy chain; if the disease is Hashimoto's disease, primary myxoedema or thyrotoxicosis, the antigen is thyroid antigen; if the disease is rheumatoid arthritis, the antigen is type II collagen or a heat shock protein (HSP); if the disease is thyroiditis, the antigen is thyroglobulin; if the disease is Behcet's disease, the antigen is Sag, HLA-B44, B51, or HSP65; if the disease is Coeliac disease/Dermatitis herpetiformis, the antigen is gliadin or the α fraction thereof; and if the disease is demyelinating disease, the antigen is myelin.

31. A method according to any one of Claims 1 to 22 for treating an allergic disease or condition in the patient.

32. A method according to Claim 31 wherein the allergic disease or condition is allergic asthma.

33. A method according to Claim 31 or 32, wherein the antigen is a mite allergen, a dust allergen, a cat allergen, a dog allergen or a horse allergen.

34. A method according to any one of Claims 1 to 33, wherein the tolerance to the antigen is to treat an aberrant or undesired immune or inflammatory response to the antigen in the patient.

35. A method according to Claim 34 wherein the aberrant or undesired immune or inflammatory response involves a deficiency in IL-10 production.

36. A composition comprising an agent which raises the effective cAMP concentration in a monocyte cell and granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof.

37. A composition according to Claim 36 wherein the agent which raises the effective cAMP concentration in a monocyte cell is any one or more of a prostaglandin or agonist thereof, a β-adrenergic agent, a blocker of cAMP export from the cell, forskolin or a derivative thereof, a cAMP phosphodiesterase inhibitor, a cAMP analogue or cholera toxin or a derivative or fragment thereof.

38. A composition according to Claim 37 wherein the blocker of cAMP export from the cell is probenicid or progesterone.

39. A composition according to Claim 37 wherein the cAMP analogue is Sp-adenosine 3′,5′-cyclic monophosphorothioate or 8-bromoadenosine 3′,5′ cyclic monophosphate.

40. A composition according to Claim 37 wherein the prostaglandin or agonist thereof stimulates cAMP production in a monocyte.

41. A composition according to Claim 37 or 40 wherein the prostaglandin or agonist thereof is a prostaglandin E such as prostaglandin E_2 or an analogue thereof, dinoprostone, gemeprost, misoprostol, alprostadil, limaprost, butaprost, 11-deoxy PGE1, AH23848, AH13205, or a 19-hydroxy PGE.

42. A composition according to any of Claims 36 to 41 wherein the GMCSF is human GMCSF having the amino acid sequence as defined in Figure 1, or naturally occurring variants thereof.

43. A composition according to any of Claims 36 to 41 wherein the GMCSF is sargramostim.

44. A composition according to any of Claims 36 to 43 further comprising a monocyte chemotactic agent.

45. A composition according to Claim 44 wherein the monocyte chemotactic agent is MCP-1 or MIP-1α.

46. A composition according to any of Claims 36 to 45 further comprising a phosphodiesterase (PDE) inhibitor.

47. A composition according to Claim 46 wherein the PDE inhibitor is any one of 3-isobutyl-1-methylxanthine (IBMX), pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione), rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-

imidazolidinone), theophylline, or denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine).

48. A composition according to Claim 46 or 47 wherein the PDE inhibitor is selective for type IV PDE.

49. A composition according to Claim 48 wherein the PDE inhibitor selective for type IV PDE is any one of rolipram (4-[3-cyclopentyloxy-4-methoxyphenyl]-2-pyrrolidinone), CP80 633, CP102 995, CP76 593, Ro-20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone), denbufylline (1,3-di-n-butyl-7-(2-oxopropyl)-xanthine), or CDP840, RP73401 or RS33793.

50. A composition according to any one of Claims 36 to 49 for inducing tolerance to an antigen in a patient further comprising an antigen to which it is desired to induce tolerance, or a derivative thereof.

51. A pharmaceutical composition comprising the composition according to any one of Claims 36 to 50 and a pharmaceutically acceptable carrier, diluent or excipient.

52. A composition comprising an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof for use in medicine.

53. A composition according to Claim 52 further comprising an antigen to which it is desired to induce tolerance in a patient or a derivative thereof, for use in medicine.

54. A composition according to Claim 52 or 53 further comprising a monocyte chemotactic agent, for use in medicine.

55. A composition according to any one of Claims 52 to 54 further comprising a PDE inhibitor, for use in medicine.

56. Use of an agent which raises the effective cAMP concentration in a monocyte cell in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered GMCSF or a derivative thereof.

57. Use of GMCSF or a derivative thereof in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell.

58. Use of an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof in the manufacture of a medicament for inducing tolerance to an antigen in a patient.

59. Use of an agent which raises the effective cAMP concentration in a monocyte cell in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered GMCSF or a derivative thereof and the antigen or a derivative thereof.

60. Use of GMCSF or a derivative thereof in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell and the antigen or a derivative thereof.

61. Use of an antigen or a derivative thereof in the manufacture of a medicament for inducing tolerance to the antigen in a patient wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof.

62. Use of an agent which raises the effective concentration of cAMP in a monocyte cell and GMCSF or a derivative thereof in the manufacture of a medicament for inducing tolerance to an antigen in a patient wherein the patient is administered the antigen or a derivative thereof.

63. Use of GMCSF or a derivative thereof and an antigen or a derivative thereof in the manufacture of a medicament for inducing tolerance to the antigen in a patient wherein the patient is administered an agent which raises the effective cAMP concentration in a monocyte cell.

64. Use of an agent which raises the effective cAMP concentration in a monocyte cell and an antigen or a derivative thereof in the manufacture of a medicament for inducing tolerance to the antigen in a patient wherein the patient is administered GMCSF or a derivative thereof.

65. Use of an agent which raises the effective cAMP concentration in a monocyte cell, GMCSF or a derivative thereof, and an antigen or a derivative thereof in the manufacture of a medicament for inducing tolerance to the antigen in a patient.

66. A therapeutic system for inducing tolerance to an antigen in a patient, the system comprising an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof.

67. A therapeutic system according to Claim 66 further comprising an antigen to which it is desired to induce tolerance.

68. A therapeutic system according to Claim 66 or 67 further comprising a monocyte chemotactic agent and/or a PDE inhibitor.

69. A therapeutic system according to any of Claims 66 to 68 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is in a preparation for administration locally at a site where tolerance is required.

70. A therapeutic system according to any of Claims 66 to 68 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is in a preparation for systemic administration.

71. A therapeutic system according to any of Claims 66 to 68 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is in a preparation for oral administration.

72. A therapeutic system according to any of Claims 66 to 68 wherein one or more of the agent which raises the effective cAMP concentration in a monocyte cell, the GMCSF or derivative thereof, the monocyte chemotactic agent, the PDE inhibitor and the antigen or derivative thereof is formulated as a suppository or capsule.

73. A method of stimulating or enhancing granulysin expression in cells of the macrophage/monocyte lineage comprising administering to the cells an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof.

74. A method of treating a viral infection in a patient comprising administering to the patient an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof.

75. A method according to Claim 74 wherein the viral infection is a herpes simplex virus infection or a human papilloma virus infection.

76. A method according to Claim 75 wherein the herpes simplex virus infection is a cold sore.

77. A method according to Claim 75 wherein the human papilloma virus infection is a wart.

78. A method of stimulating or enhancing IL-10 expression in, and secretion from, cells of the macrophage/monocyte lineage comprising administering to the cells an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof.

79. A method of treating a tumour in a patient comprising administering to the patient an agent which raises the effective cAMP concentration in a monocyte cell and GMCSF or a derivative thereof.

80. A method according to any one of Claims 73 to 79 further comprising administering a monocyte chemotactic agent.

81. A method according to any one of Claims 73 to 80 further comprising administering a PDE inhibitor.